Serum HbA_{1c} Levels and Exercise Capacity in Diabetic Patients

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SUMMARY

It is well known that cardiovascular morbidity and mortality are high in diabetic patients. Cardiac involvement is silent and early and these diabetic patients generally complain of chronic fatigue. This study was designed to evaluate the relation between glycemic control and exercise capacity in 330 diabetic patients who have no cardiac symptoms by sustaining dynamic exercise. After a cardiac examination, patients with coronary heart disease, ECG abnormalities, cardiac failure, valvular disease, cerebrovascular disease, peripheral artery disease, anaemia and peripheral neuropathy were excluded. Plasma HbA_{1c} and lipid levels were obtained and a symptom limited exercise test based on "Bruce Protocol" was performed on all patients. Plasma HbA_{1c} levels were significantly increased in smokers and in hypercholesterolemic patients ($p<0.001$, $p=0.006$). A moderate correlation between exercise capacity and HbA_{1c} levels, and a weak correlation between duration of diabetes, age, sex, hypertension and plasma lipids were obtained. Multivariant regression analys is revealed that only HbA_{1c} and hypercholesterolemia affected exercise capacity independently ($r=-0.54$ $r=-0.30$). In conclusion, poor glycemic control in diabetic patients causes earlier cellular involvement. Because of the high affinity of HbA_{1c} to oxygen, the energy metabolism of the cell is affected, with a clinical correlation betreen chronic fatigue and worsening exercise capacity. (Jpn Heart J 2001; 42: 607-616)

Key words: Diabetes, HbA1c, Exercise capacity

IT is well known that diabetes is an important and independent risk factor for cardiovascular mortality and morbidity. It is said that cardiovascular disorders are more frequent in diabetic patients and cardiac disorders rank first among the causes of death in this population. Microvascular complications, excluding epicardial coronary artery stenosis, occur earlier and tend to be silent.[1-3] Epidemiologic studies show that diabetes increases the prevalence congestive heart failure itself without hypertension and coronary heart disease.[4-5] Diabetic cardiomyopathy is mentioned as a distinct entity also.[6] Latent left ventricular dysfunction has been reported in some studies using noninvasive techniques.[7-10] Diastolic dys-

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function has been shown to be impaired first in diabetic patients in studies comparing them with nondiabetics.[9-11] Left ventricular function is assessed by echocardiography after isometric exercise in some studies. There are a few studies concerning dynamic exercise capacity and its relation with HbA_{1c} in diabetic patients. We wanted to find out if there is a relation between glycemic control and exercise capacity in diabetic patients who have no cardiac symptoms, by sustaining dynamic exercise.

MATERIALS AND METHODS

The study population was comprised 330 patients from the Diabetics Outpatient Department accepted as diabetics according to WHO criteria.[12] The mean age was 51.7±9.3 with a distribution between 38-72 years. The female to male ratio was 160/170. After the echocardiograpic and cardiac examinations patients with cardiac symptoms, coronary heart disease, ischemia or arrhythmia on resting ECG, symptoms and signs of cardiac failure, valvular heart disease, cerebrovascular disease, anaemia (Hb<11), peripheral artery disease or peripheral neuropathy, patients taking drugs which can affect cardiac function, patients who have grade 2 or higher degree of hypertension, and patients with ketonuria and ketoacidosis were excluded. Venous blood samples were taken after a fasting period of 12 hours. Plasma HbA_{1c}, total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL) levels were analysed. TC and TG were analysed with a standard enzymatic method (Boehringer Mannheim GmBH Germany) and expressed as mg/d*l*. HDL was measured after the precipitation of other cholesterol fragments and also expressed as mg/d*l*.[13] LDL cholesterol was calculated using the Friedewald formula.[14] HbA_{1c} was analysed with Bio-Rad DIAMAT glycosylated hemoglobin analyser system and expressed as percentiles.[15] Values between 4.5-6.5% were accepted as normal for HbA_{1c}. The exercise test was performed according to the Bruce protocol using a Quinton 6000 model exercise test machine. An ECG record with standard 12 leads and blood pressure and pulse rate were performed before and every three minutes. during the exercise test.The ECG, pulse rate and blood pressure of the patients were examined for 5 minutes after the test. A horizontal or a downsloping depression of the ST segment of 0.1 mV or more on two consequent leads during or after the exercise, new fasicular blocks, or onset of typical angina proved the test to be positive. The patients who had a positive stress test were excluded.

Statistical Analysis

The patients Charactesistics are expressed as the mean+standard deviation and % frequency. The effects on exercise capacity were analysed by Pearson correlation test. To determine in the patients who revealed a significant relation by the Pearson correlation test multinominal logistic regression analysis was performed if there was an independent factor. The relation between HbA_{1c} and nominal values was evaluated by an independent *t*-test after normalization of the nominal distribution and the relation between HbA_{1c} and numeric values, by Pearson correlation test and multinominal logistic regression test. A $p<0.05$ indicated statistical significance. Statistical analysis was performed using an SPSS 9.0 computer programme

Results

Fifty-five (25 females/30 males) of the 330 patients selected for the study from our Diabetics outpatient clinic department were excluded for not meeting the inclusion criteria or ischemic findings on their exercise electrocardiograms. The remaining 275 patients (135 females/140 males, mean age 52.9±8.9, range 38-72years) were included in the statistical analysis. The mean duration of diabetes was 6.8±6.9 (1-29) years. Blood glucose regulation was achieved by oral hypoglycemic agents in 260 patients and by insulin injections in 15 patients. The clinical characteristics of the patients summarised in Table I, show 38.2% were hypertensive, 36.4% were hypercholesterolemic, 16.4% smokers, 41.8% had familial predisposition to atherosclerosis, 16.4% were under heavy stress, and 15.6% had proteinuria. The HbA_{1c} and lipid profiles of the patients are shown in Table II while Table III summarizes the exercise test outcomes of the patients according to the Bruce protocol. The statistical relation between the clinical characteristics and HbA_{1c} levels is summarized in Table IV and shows that, HbA_{1c} levels were significantly higher in patients with hypercholesterolemia, proteinuria, and in patients who are smokers and under heavy stress. The assessment of exercise capacity of the patients after they were grouped according to their clinical charactesistics is shown in Table V. The relation between HbA_{1c} levels and exercise capacity, lipid values, initial and peak pulse values, mean blood pressure values and age were evaluated by the Pearson correlation test. The results are shown in Table VI. After obtaining correlation outputs, our multinominal logistic regression analysis to determine the independent factors affecting exercise capacity, revealed that only HbA_{1c} and hypercholesterolemia affected exercise capacity independently (r=-0.54, $p<0.001$; r=-0.2, p=0.04 respectively). The Figure shows the linear correlation between exercise capacity and HbA_{1c}. As shown in the Figure and Table VI, we obtained a moderate negative correlation

Table I. Basic Features of the Patients

		(%)
Age (Mean±SD) years	52.9±8.9	
Mean duration of diabetes (year)	6.8±6.9	
Gender (Female /Male)	135/140	
Hypertension (mild) (+/-)	105/170	38.2
Hypercholesterolemia (+/-)	100/175	36.4
Smoking (+/-)	45/230	16.4
Heredity (+/-)	115/160	41.8
Stress (+/-)	45/230	16.4
Proteinuria (+/-)	43/232	15.6

Table II. Lipid and HbA_{1c} levels of All Patients

	Distribution	Mean±SD
HbA1c (%)	4.1-13.1	6.88±2.01
TC (mg/d*l*)	140-342	224.54±45.81
LDL (mg/d*l*)	70-210	143.11±34.95
HDL (mg/d*l*)	14-72	43.97±12.04
VLDL (mg/d*l*)	16-101	34.92±16.6
TG (mg/d*l*)	58-504	190.65±113.06

TC=total cholesterol; HDL=High density lipoprotein; LDL=low density lipoprotein; VLDL=very low density lipoprotein; TG=triglyceride.

Table III. Exercise Test Outcomes

	Distribution	Mean±SD
Exercise capacity (met)	6-16.5	9.57±2.32
Pulse initial (dk da)	64-122	86.81±11.54
MBP initial (mmHg)	80-120	97.66±9.21
Pulse peak (rate/min.)	131-192	169.36±10.98
MBP peak (mmHg)	90-133.33	111.60±10.55

MBP=mean blood pressure.

Table IV. HbA_{1c} Levels According to Clinical Features

	HbA_{1c} %		*P*
	(+)	(-)	
Hypercholesterolemia (+/-)	7.92±2.2	6.3±1.6	0.001
Smoking (+/-)	7.95±2.9	6.7±1.7	0.006
Stress (+/-)	7.51±1.5	6.75±2.1	0.02
Proteinuria (+/-)	7.37±2.2.	6.74±1.95	0.03
Hypertension (+/-)	7.14±1.5	6.72±2.2	NS
Heredity (+/-)	7.1±1.8	6.7±2.2	NS
Gender (female/male)	6.7±2.1	7.06±1.8	NS
Treatment type (insulin/OAD)	6.86±2.03	7.1±1.9	NS

OAD=oral anti diabetic; NS=non significant. Independent *t*-test is used in analyses.

Table V. Exercise Capacity According to Clinical Features

	Exercise capacity (met) (+)	(-)	*P*
Hypercholesterolemia (+/-)	7.6±1.7	9.2±1.88	0.001
Hypertension (+/-)	8.09±1.9	8.9±1.9	0.01
Gender (female/male)	7.88±1.73	9.32±1.98	0.001
Stress (+/-)	7.77±2.06	8.78±1.9	0.002
Smoking (+/-)	8.44±1.97	8.65±1.99	NS
Heredity (+/-)	8.47±2.1	8.71±1.9	NS
Proteinuria (+/-)	8.4±2.1	8.67±1.9	NS
Treatment type (insulin/OAD)	8.67±1.94	7.67±2.6	NS

OAD=oral anti diabetic; NS=non significant. Independent *t*-test is used in analyses.

Table VI. Pearson Correlation Outputs of HbA_{1c} and Exercise Capacity

	Exercise capacity	DM duration	Pulse	MBP mmHg	TC	LDL	HDL	TG	Age
HbA_{1c}	-0.58* 0.001+	0.19* 0.001+	-0.16* 0.008+	NS	0.25* 0.001+	0.17* 0.004	-0.18* 0.002	0.30* 0.001+	NS
Exercise Capacity		-0.36* 0.001+	NS	NS	-0.3* 0.001+	-0.2* 0.001+	0.2* 0.001+	NS	-0.24* 0.001+

(*= r; +=*p* value) DM=diabetes mellitus; MBP=mean blood pressure; TC=total cholesterol; LDL=low density lipoprotein; HDL=high density lipoprotein; TG=triglyceride.

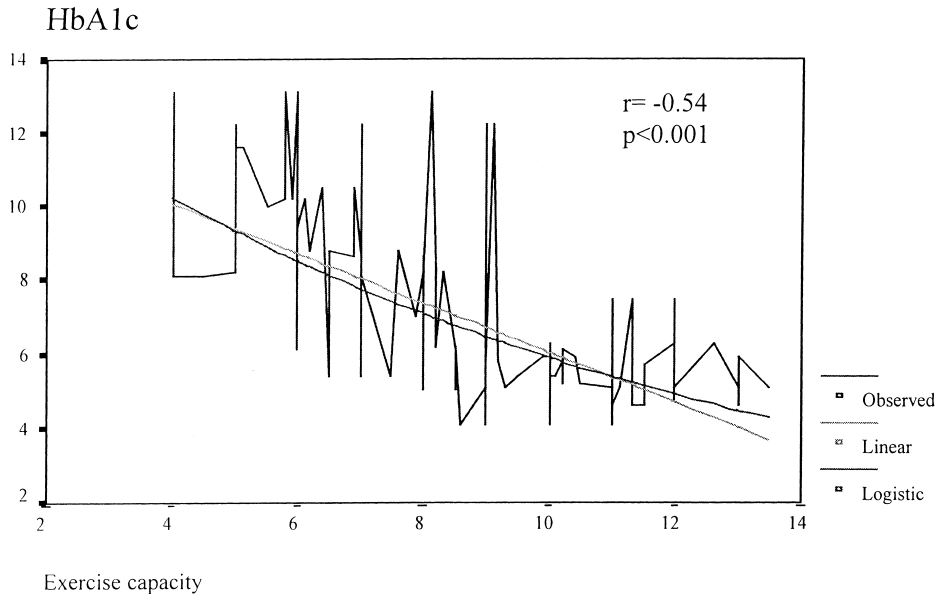

Figure. Regression graphic between HbA_{1c} and exercise capacity.

between HbA_{1c} and exercise capacity (r=0.54).

DISCUSSION

Although it is well known that diabetic patients who have poor metabolic control complain about fatigue and weakness, there have only been a few studies that examined dynamic exercise tolerance in diabetic patients and its relation to HbA_{1c}.[16,17,20] In this study we evaluated the effect of HbA_{1c} on exercise tolerance, the clinical factors affecting the HbA_{1c} levels, and their relation with exercise capacity in diabetic patients. There are several echocardiographic and scintigraphic studies evaluating HbA_{1c} and left ventricular function in the literature.[5-9]

Isometrical exercise scintigraphic studies have shown impaired left ventricular systolic function and this has been correlated to unlikely changes in myocardial energy metabolism.[18,19,40] These studies also revealed that the ejection fraction decreased in 30-35% of the diabetic patients and this decrease was not associated with the duration of the diabetes, autonomic nervous system dysfunction, age or gender.[7,21] It is known that left ventricular diastolic function is impaired before systolic function and the alteration in diastolic fill and enddiastolic diameter is decreased. Huikuri, *et al*[7] assessed the change in left ventricular fractional shortening with handgrip exercise and found that the decrease in fractional shortening in patients with high HbA_{1c} levels was more significant. Left ventricular dysfunction in asymptomatic diabetic patients is thought not to be associated with either an increase in afterload or a decrease in contractility, but with subclinical diabetic al cardiomyopathy or a decrease in left ventricular diastolic filling.[22,23]

The autopsy studies on diabetic patients who died because of congestive heart failure revealed histopathologic changes in intramural coronary arteries, capillaries and in the interstitium, although epicardial arteries seemed to be normal.[24,25] Significant changes in myocardial energy metabolism have also been mentioned in experimental studies as opposed to changes in diabetic myocardium, intramural vessels, and interstitium.[26-28] In a study using intracoronary papaverine and acetylcholine, coronary vascular reserve was found to be decreased and endothelin associated vasodilatation to be impaired.[30]

As shown in Table I, patients with a percentage ranging between 15.6% and 41.8% had a major atherosclerotic risk factor other than diabetes. HbA_{1c} levels were found to be significantly higher in patients with hypercholesterolemia, smoking habits, stress and proteinuria. A direct relationship was observed between hypercholesterolemia and glycemic control. One can claim that glycemic control is poor in a diabetic if the patient has hypercholesterolemia. Our find-

ings also revealed that smoking habits and stress impairs the metabolic control of glycemia.

Hypertension, gender, therapeutical regime, and heredity (a first degree relative with diabetes or coronary heart disease) seemed to not affect HbA_{1c} levels (Table IV). When their effects on exercise capacity were considered, only hypercholesterolemia and stress tended to be correlated. Despite the fact that smoking and proteinuria affected HbA_{1c} levels, neither affected exercise capacity. Hypertension was also found to affect exercise capacity as the hypertensive patients had a lower exercise capacity than did the normotensives. Gender affected exercise capacity significantly since males tended to have a higher exercise capacity than females. This can be explained by the fact that men have a higher physical performance level than the women. Because of the high affinity to oxygen, an increase in glycosylated hemoglobin impairs oxygen transport in diabetic patients, resulting in chronic fatigue and decreased exercise capacity. A moderate negative linear correlation between HbA_{1c} levels and exercise capacity was obtained after performing correlation and logistic regression analyses and hypercholesterolemia was found to correlate positively with HbA_{1c} levels. As shown in TableVI, there was a weak but significant negative correlation between hypercholesterolemia and exercise capacity. Baum, *et al*[31] have found a negative correlation between exercise duration and HbA_{1c} levels which was compatible with our findings.

It is well known that, like the high affinity of glycosylated hemoglobin to oxygen, lipid peroxidation also effects energy metabolism and impairs oxygen delivery and use, and even the compensatory mechanism of an increase in 2,3 diphosphoglycerate levels can not achieve a decrease in the affinity of HbA_{1c} to oxygen.[32,33] In the studies evaluating left ventricular function by dynamic exercise and scintigraphic methods, a significant correlation between glycemic control level and left ventricular function was found.[9,19] More significant increases occur in blood pressure, heart rate and myocardial oxygen demand with dynamic exercise than with the isometric exercise. Thus, myocardial ischemia resulting from a small vessel disease, may be not from an epicardial coronary artery disease, other than the fact of high glycosylated hemoglobin, might be playing a role in the decreased left ventricular contractile response to dynamic exercise in diabetic patients.[24,33]

The frequency of silent myocardial ischemia is 20% among diabetes patients. Exercise testing is a simple and inexpensive diagnostic modality that can identify silent myocardial ischemia. Although, at the begining of our study, we excluded patients with coronary heart disease, we determined silent myocardial ischemia in 55 patients (17%). Even though we have excluded silent myocardial patients during our study, there might be few patients which are silent myocardial ischemia because of false negative results among the patients whose exercise

capacity is low. Moreover, we believe that the number of those facts are few. There were some patients in the study group outside of the regression line at the Figure 1. When we examine the reason why HbA_{1c} and exercise capacity do not conform to the study results, we have determined the main factors as age, diabetes duration and gender of the patients. Even if age and diabetes duration is an effective factor for exercise capacity, it is seen during the analysis of logistic regression that level of HbA_{1c} affects exercise capasity free from other factors (Figure). We have determined that exercise capasity is 9.47±1.64 MET for patients with HbA_{1c} <7% and 7±1.52 MET for those with HbA_{1c}>7%. Thus, when HbA_{1c}>7%, exercise capacity is obviously affected.

We did not observe whether exercise capacity recovered or not when HbA_{1c} levels were decreased to normal levels after strict glycemic control in patients with high HbA_{1c} levels. The literature reveals howevcr that after good glycemic control is achieved in poorly controlled patients, the ejection fraction improves.[34] Thusen, *et al*[16] demonstrated that exercise capacity increased 24% after good glycemic control, whereas blood pressure and heart rate did not change. Fisher, *et al*[35] have found that good glycemic conrtol achieved the restoration of left ventricular echocardiographic hemodynamic parameters during isometric exercise.

In scintigraphic studies of patients who experience a worsening ejection fraction with exercise, 28-30% of the patients showed perfusion defect, whereas only 8-10% had an angiographically proven coronary stenosis.[3,36] Although asymptomatic coronary artery disease is more frequent in diabetics, many studies remind us that decreased exercise capacity and impaired left ventricular ejection fraction with exercise can not be completely attributed to this silent ischemia in these patients.[37] If good glycemic control is achieved in daibetic patients with a known coronary artery disease, no decrease in exercise capacity and no impairment in left ventricular ejection fraction with exercise can be found.[21]

The most probable explanation for exercise induced left ventricular dysfunction is that hypercholesterolemia, hyperglycemia, diabetes and other metabolic disturbances impair myocardial cellular function, interstitial connective tissue structure and microcirculation. Some studies have demonstrated that Ca^{+2}-ATPase activity is depressed in patients with poor glycemic control, which can be responsible for the systolic and diastolic left ventricular dysfunction in these patients and that the functions improve when glycemic control is achieved.[27,38,39]

If glycemic control is poor in diabetic patients, the affects of the disease at the microvascular and cellular levels occur much earlier. Because of the high affinity of HbA_{1c} to oxygen, cellular energy methabolism is affected first , resulting in physiopathologic impairment at the cellular level before the major complications of the disease occur. The first clinical implication of this phenomenon is chronic fatigue in these patients along with a severe decrease in their exercise

capacity. Although it is not known exactly how HbA_{1c} affects the exercise capacity, many different ideas have bean put forward. Our study does not demanstrate a correlation between HbA_{1c} and exercise capacity, but the finding may be a guide for clinical observation.

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